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Gene therapy for cancer using tumour-specific prodrug activation.

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Current treatments for metastatic malignant disease are often ineffective. One of the most promising of the selective genetic strategies against cancer is VDEPT (virally directed enzyme prodrug therapy). This uses a viral vector to carry a prodrug-activating enzyme gene into both tumour and normal cells. By linking the foreign gene downstream of tumour-specific transcription units, tumour-specific expression of the foreign enzyme gene can be achieved. We have developed a genetic therapy strategy using VDEPT against cancers that overexpress the oncogene ERBB2. This occurs in approximately one-third of breast and pancreatic tumours (and in a smaller proportion of other tumours) and involves transcriptional up-regulation of the ERBB2 gene with or without gene amplification. We have constructed a chimeric minigene consisting of the proximal ERBB2 promoter linked to the gene encoding cytosine deaminase, an enzyme that can deaminate the prodrug 5-fluorocytosine (5-FC) to form cytotoxic 5-fluorouracil (5-FU). We have constructed a double-copy recombinant retrovirus to deliver the enzyme gene under the control of the ERBB2 promoter into a panel of ERBB2 expression-positive (ERBB2+) and -negative (ERBB2-) pancreatic and breast cell lines. Cytosine deaminase activity was high in ERBB2+ transduced cells but was not detected in ERBB2- transduced cells. Significant cell death was observed in ERBB2+ transduced cells treated with 5-FC whereas ERBB2- cells were not affected. Hence we present a novel gene therapy strategy that is potentially tumour-specific and could be used against a range of tumour types that overexpress the ERBB2 oncogene.

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